REMARKS

This is in response to the official action dated September 14, 2010. Reconsideration in view of the following is respectfully requested.

Claim Status

Claims 1, 3, 6-15 and 17-24 are pending in the application and stand rejected. Claims 1, 3, 6, 8-9, 17-18, 23 and 24 have been amended. Claims 2, 4-5, 7, 10-11, 16, and 20 were cancelled.

Listing of antibodies/peptides used for raising antibodies

A list of the peptides used to raise antibodies recited in current claims and their sources are attached (SEQ ID No:2-5). All derive from isoform III.

Claim Rejections* - 35 *USC* § 112 *1st paragraph/written description

Claims 17 and 18

Claim 17 has been amended deleting the objected-to part "administering to a[n] patient"; likewise dependent claim 18.

Claim Rejections* - 35 *USC* § 112 *1st paragraph/written description

Claims 1, 3, 6-11, 17-24

SEQ ID No: 2-5 of elastase isoform III

To further procecution, all claims involving a selection of synthetic peptides have been limited to one or more of SEQ ID No: 2-5, all of which recognize isoform III. In particular, this includes claim 1, claim 7 now redundant is deleted accordingly, and its dependent claims 8 and 9 are renumbered to depend from claim 1 instead. Similarly claims 6 and 17 are directed to SEQ ID No: 2-5. These sequences derive from elastase isoform III.

Notably, the sequence of each peptide itself shows which particular isoform it is derived from and, once specific binding to an elastase has been shown, which isoform antibodies raised against such a peptide will recognize. Accordingly, references to elastase 1 or other elastase

isoforms have been deleted in all claims including claims 3 and 6. Further, the elastase II alternative has been deleted from claim 24.

Claim 17 has been amended to reflect that SEQ ID No: 2-5 all derive from the same elastase isoform, deleting the "several elastases" part.

Detection in body fluids is taught in the specification

Applicant believes to have enabled the invention so the skilled person can carry it out without undue experimentation. The determination in body fluid is taught in the specification in great detail clearly showing the applicant was in possession of the invention. Applicant directs examiner's attention to pages 4, 8-9 (example 3) and 10-11 (example 6, which includes serum, a body fluid), of the present application, see relevant excerpts below. Both examples demonstrate specificity of the results.

Page 4 excerpt:

It was shown that antibodies against the peptides A-V-K-E-G-P-E-Q-V-I-P-I-N, Y-T-N-G-P-L-P-D-K-L-Q-Q-A-R, R-S-G-C-N-G-D-S-G-G-P-L-N, G-P-L-N-C-P-T-E-D-G-G-W-Q, G-T-E-A-G-K-N-S-W-P-S-Q-I, H-N-L-S-Q-N-D-G-T-E-Q-Y-V, W-G-K-T-K-T-N-G-Q-L-A, V-S-S-R-G-C-N-V-S-R-K-P-T, G-G-E-E-A-R-P-N-S-W-P-W-Q, S-S-S-R-T-Y-R-V-G-L-G-R-H-N, K-D-W-N-S-N-Q-I-G-K-G-N-D, G-P-L-N-C-Q-A-S-D-G-R-W, G-A-L-P-D-D-L-K-Q-G-R-L, S-L-Q-Y-E-K-S-G-S-F-Y, F-G-C-N-T-R-R-K-P-T-V-F-T react highly specifically with the iso-forms of the pancreas elastase and do not react unspecifically with other stool components.

Excerpts page 8 & 9:

Implementation example 3 - Identification of elastase 1 in stool using the invention antibody in an ELISA

The elastase 1 in serum samples or in stool samples is identified in a fixed phase enzyme immuno-assay based on the sandwich technique. A polyclonal antibody that is targeted against epitopes of elastase 1 is dissolved in a carbonate/bicarbonate

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is measured. The intensity of the colour reaction is proportional to the elastase 1 concentration of the sample.

Excerpts pages 10 & 11:

Implementation example 6 - Identification of the pancreas elastase in stool and serum using the antibodies in the invention

The elastase in serum, plasma or stool is identified using a fixed-phase ELISA based on the sandwich technique. For this purpose individual invention antibodies or a corresponding mixture of several of the invention antibodies are dissolved in a carbonate/bicarbonate buffer solution pH 9,6 and placed in the

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measured. The intensity of the colour reaction is proportional to the elastase concentration in the sample.

Parallel elastase isoform detection is optional according to specification

A novel procedure able to detect at least one diagnostically relevant iso-form in a diagnostic test is provided, and the specification also describes parallel detection. However, simultaneous binding of multiple isoforms is not required for the functioning of the claimed diagnostic procedure.

Notably, claim 1 is directed to "**one or more**" pancreatic elastase iso-enzyme", and does not require binding of the peptides to all elastase isoforms.

Patent law does not require applicant to choose a particular mode detecting multiple isoforms in parallel even if it is be possible and may be preferred in certain diagnostic situations. The invention provides procedures that can detect one or more diagnostically relevant elastase isoform with specificity in body fluids using peptides previously not know to be useful for diagnostic purposes. There is no need to detect all isoforms in parallel. Some peptides detect one isoform, some another. Which isoform is detected can be easily determined using standard methods by using the peptide sequence. Current claims are directed to peptides derived from elastase III isoforms, see list attached, that can raise specific elastase antibodies.

Diagnostic procedures to detect elastase have been employed in diagnosis in the past, be it with less specificity and with problems arising in body fluids. An alternative method detecting an elastase isoform with specificity in body fluids therefore is a valid, workable and useful procedure, which notably has been described in great detail in the original application as shown e.g. in the excerpts above (in particular, a polyclonal antibody in example 3, or the individual antibody variant of example 6). Notably, SEQ ID No: 1 is not recognized by the claimed procedures.

As addressed in the specification of the present application, see relevant excerpt of page 4 below, an object of the invention is the use of elastase antibodies to identify and quantify the various elastase iso-enzymes .

Another subject of the invention is the use of the elastase antibodies in the invention for the identification and quantification of al known elastase iso-enzymes in body fluids and in stool. The invention is therefore also relevant in terms of identification systems, particularly an immune-chemical identification system to establish the functionality of the pancreas as an aid to the recognition of functional disorders of this organ. For this purpose the specific antibodies can be

Notably, it is not necessary to identify the iso-forms **in parallel**/at the same time in **one** procedure. For example, one assay could determine elastase II, and another elastase III in stool and body fluids with high specificity, which was previously not possible. As discussed above, current claims are directed to peptides of isoform III and methods employing such peptides.

Claim Rejections* - 35 *USC* § 112 *2nd paragraph/indefiniteness

Claims 1, 3, 6-11, 17-24

Claims 1 and dependent claims – unclear interrelationship

****between antibodies against peptides & antibodies obtained by immunizing animals with subunits in claim 3***

Claim 3 has been amended using the wording of claim 1, i.e. "synthetic peptides of claim 1" rather than "antigens from …. elastase"; and the redundancy in regard of SEQ ID NO:1 has been addressed by deleting the relevant passage in claim 3 (the corresponding passage in claim 1 remains). The "monoclonal [antibodies]" of claim 3 have been deleted. Furthermore, typos and grammar issues have been addressed (use of singular/plural in the animal list).

**** between polyclonal abs of claim 1 & monoclonal abs of claim 3***

Claims 3 & 20 have been amended deleting the "monoclonal [antibodies]" as requested.

**** between claim 1 and "administered in claim 23 (no antecedent basis)***

Claim 23 has been amended deleting "administered".

In claims 3, 20 and 23 depending from claim 1, "using" is not a valid method step/"the" content lacks antecedent basis

The claims have been amended for consistency in the method step language as detailed above and claim 1 now provides antecedent basis.

Improper Markush language

The Markush language in claims 1, 3, 17 and 23 has been corrected using the format as suggested by the examiner.

Claim 20- myeloma

The claim has been cancelled.

Claim 21 and 22 –no further limitation/duplicative

The amendments render Claims 21 and 22 superfluous, both claims are cancelled accordingly.

Claim 18- recital of immunological test kit

The test kit is recited as requested by the examiner.
Further, claim 18 now recites 2 "or more" antibodies. From the specification and claims, for example claims 1 or 7, it is apparent that a number of combinations, e.g. 4, are possible.

Further claim amendments of claims correct typographical or grammatical errors.

Claim Rejections - 35 U.S.C. § 102 Novelty

Claims 6-8, 10 & 22 in view of Sziegoleit in light of the instant disclosure

Claim 7 is redundant in view of current amendments and cancelled accordingly. Claim 6 has been amended reciting the synthetic peptides of claim1 which should obviate the examiner's lack of novelty rejection. Claim 8 dependent on claim 1 likewise is novel. Claims 10 and 22 have been cancelled.

Claim Rejections - 35 U.S.C. § 102 Novelty

Claims 6-8, 10 & 22 in view of Scheefers/US 5,622,837 in light of the instant disclosure

Claims 6 has been amended reciting the synthetic peptides of claim1 which should obviate the examiner's lack of novelty rejection. Claim 8 dependent on claim 1 likewise is novel. Claims 10, 11 and 22 have been cancelled.

Claim Rejections - 35 U.S.C. § 103 Obviousness

Claims 1, 3, 6-15, 17-24 over the combined teachings of Scheefers et al., Tani et al., and Harlow et al.

Scheefer discloses an elastase and an assay used in serum and stool to detect it. Tani discloses elastase III. Harlow relates to synthetic peptide design to raise antibodies.

Notably, the claims are directed to antibodies "raised against … synthetic peptides …", so that antibodies to purified enzyme or fragments thereof are not covered by the present claims. More importantly, instant antibodies do **not** recognize Thr-Met-Val-Ala-Gly-Gly-Asp-Ile-Arg (SEQ ID NO: 1), which is the epitope identified and described in the Scheefer patent.

The present invention at least provides alternative peptides/related antibodies useful for diagnostic purposes.

Unexpectedly, antibodies raised against peptides **different from SEQ ID No: 1** (which was known to be useful in the detection of elastase in stool from Scheefer) are able to specifically recognize partially digested elastase enzymes in bodily fluids/stool as shown in the present application. Notably, the present diagnostic method is the first to specifically detect an elastase isoform without recognizing SEQ ID No:1, i.e. against another elastase isoform. Significantly the present application describes using antibodies raised against individual peptides which when used in the described routine procedure clearly show specificity. None of these peptides has been suggested by the prior art documents alone or in combination, nor has any of these documents provided any teaching these may provide specific binding or be diagnostically useful.

Furthermore, the presently claimed invention has advantages not suggested by the prior art documents alone or in combination. The elastase isoform detected by the claimed procedures had not been previously detected, nor was it clear how to apply Harlow's peptide design to elastase III to provide specific and diagnostically relevant antibodies.

Prior to the present invention it was unpredictable if it even was possible to raise antibodies against the relevant recognized isoform that would be selective for elastase enzymes rather than other proteins, or would be selective for human elastase, or would be diagnostically useful.

The usefulness and advantages of the presently claimed antibodies are confirmed for example in the studies of Prof. Keim and Dr. Weiss.

Dr. Keim's studies clearly demonstrate the diagnostic relevance for antibodies of present claims ("BIOSERV"); furthermore, Dr. Keim demonstrates superior sensitivity (77.8% versus 68.9%) and comparatively high specificity, see relevant excerpt below.

Clinical Value of a New Fecal Elastase Test for Detection of Chronic Pancreatitis

Volker Keim, Niels Teich, and Joachim Moessner

Published in: Clinical Laboratory, Vol. 49, No. 5+6, 2003; pp. 209 – 215

Sensitivities:		
	BIOSERV:	77,8%
	Schebo:	68,9%
	Chymotrypsin:	57,8%
Specificities:		
	BIOSERV:	76,0%
	Schebo:	77,2%
	Chymotrypsin:	52,7%

Dr. Weiss used commercially available antibodies according to the present claims directed against elastases III a and III b which do not detect elastase I or II and shows that the

antibodies only react to the corresponding isoforms and do not cross react with pig elastase, see relevant excerpt below.

Assessment of Isoform specificity of a polyclonal Elastase ELISA

F U Weiss1, M Ruthenbürger1, E Hammer2, U Völker2, M M Lerch1. Published in: Journal of Pediatric Gastroenterology and Nutrition 43:E32 # 58, 2006

Results: In 1D Western blots of pancreatic juice all three polyclonal antisera against human Elastase detected a single ~30kDa protein. Immunoprecipitates with these antibodies exhibited elastase activity as determined with the fluorogenic Elastase substrate. In 2D-Westernblots (pH3-10) proteins in the molecular weight range of ~30 kDa were separated into a number of spots of different isoelectric points (pI). MALDI-TOF-MS-Analysis of these spots revealed the presence of pancreatic Elastase IIIA and IIIB isoforms, but not Elastase II or Elastase I isoforms. Western blot analysis of pancreatin from pig pancreas revealed no cross-reactivity with any of the three antisera tested.

Conclusion: All three commercial antibodies that are used in a polyclonal Elastase ELISA preferentially detect human Elastase Isoforms IIIA and IIIB, and do not cross-react with pig pancreatin. At present differences concerning expression and specific function of PA II or PA III isoforms are still unknown, but we could demonstrate, that PA III isoforms clearly possess Elastase activity as determined by a fluorogenic Elastase substrate. Elastase I ia not an enzyme expressed in the adult human pancreas and should therefore not be referred to in commercial test kits for exocrine pancreatic function.

Accordingly applicant believes the invention is not obvious.

Wherefore, allowance of all claims is earnestly solicited.

Respectfully submitted,

NORRIS McLAUGHLIN & MARCUS, P.A.

By /Bruce S. Londa/
Bruce S. Londa
Norris McLaughlin & Marcus, P.A.
Attorney for Applicant(s)
Reg. No. 33531

875 Third Avenue - 8th Floor
New York, New York 10022
Phone: (212) 808-0700
Fax: (212) 808 – 0844

List of peptides and source/specificity

AVKEGPEQVIPIN (SEQ ID NO: 2)	Elastase 3B Isoform
YTNGPLPDKLQQAR (SEQ ID NO: 3)	Elastase 3A Preproprotein
RSGCNGDSGGPLN (SEQ ID NO: 5)	Elastase 3B Isoform
GPLNCPTEDGGWQ (SEQ ID NO: 4)	Elastase 3A Isoform